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SCIENTISTS FIND KEY IMMUNE SYSTEM GENE

STANFORD—

In research with profound implications for immunology, a team of scientists—led by a medical microbiologist from Stanford University—has isolated the elusive gene believed to regulate the body's response to tissue transplants and to infectious agents.

The effort was led by Dr. Mark Davis, assistant professor of medical microbiology at Stanford University School of Medicine.

His collaborators in the work, published simultaneously in two articles in the March 8 issue of Nature, are Dr. Stephen Hedrick of the UR ersity of California in San Diego, Ellen Nielsen of the National Institute of Allergy and Infectious Disease, and Dr. David Cohen and Joshua Kavaler in Davis' laboratory at Stanford.

The newly isolated gene had been sought unsuccessfully for at least a decade by researchers around the world, according to Davis.

The gene—a very small portion of the hereditary material, DNA—contains a blueprint for a substance produced by "T-cells," one of two major cell types responsible for the body's immune responses. The gene, which has been cloned by the researchers, codes for a substance called the T-cell receptor.

Davis' research team found the T-cell receptor gene from mice; it is known to be nearly identical to the human gene, he said. Another research group from Canada reported in the same issue of Nature32 finding a gene from humans with similar properties, he added.

To work properly, the immune system depends on two major types of cells, called B-cells and T-cells, Davis explained.

B-cells produce antibodies, molecules that participate in the body's fight against bacterial and viral disease.

T-cells play a wider variety of roles in the immune system, Davis said, including regulation of the actions of B-cells. They also control the body's response to tissue transplants, and can directly kill viruses and certain types of tumor cells, he explained.

Both B-cells and T-cells must recognize foreign substances in the body in order to carry out their jobs. They do so by means of specialized receptor molecules located in their membranes or on their surfaces.

In recent years, a lot has been learned about how B-cells perform this task by means of their antibody receptors, Davis said.

But so little has been understood about how T-cells detect invading agents that the search for the elusive T-cell receptor and its encoding gene had become a challenge to many researchers in the field, he said.

With the T-cell receptor gene finally "in hand," scientists can now begin to answer many questions about the immune system that have baffled immunologists, Davis said.

Foremost, it is now possible to learn how T-cells work—how they recognize both foreign substances and self. This should lead to a better understanding of the immune system in general and of transplant rejection and viral infection, Davis predicted.

Also, it should now be possible to figure out how many types of T-cells there are and how they differentiate, what the roles of the different T-cell types might be, how they regulate the immune response, and how they combine with B-cells to destroy disease-causing agents, Davis said.

Discovery of the T-cell receptor gene may provide more immediate clinical benefits in addition to clarifying basic unanswered questions about immune system function, said Davis. These would include the ability to identify different classes of T-cell tumors, and the potential for developing specific T-cell tumor identification markers that could aid in cancer therapy.

Davis and his colleagues used a novel, indirect method to find the T-cell receptor gene. They capitalized on their knowledge about the genes that code for B-cell antibodies in developing the approach. They also made use of the fact that B-cells do not produce any T-cell receptor.

B-cells produce antibodies, molecules that sit on the surfaces of B-cells and also rove through the body's tissues on the lookout to bind and mark for destruction invading material. Different varieties of B-cells are highly specialized to make specific antibody molecules that can latch onto a particular foreign substance, called an antigen.

Although all B-cells start out with identical antibody-coding genes, segments of these genes can be "mixed and matched" as B-cells mature. This rearrangement of DNA enables each type of B-cell to develop a "tailormade" response to a particular foreign antigen, Davis explained.

Davis and his colleagues reasoned that T-cells would also have to undergo rearrangement of their DNA in order to produce enough receptor variety to be able to specifically recognize the many different substances that can enter the body.

They also reasoned that T-cells and B-cells were actively expressing different portions of their DNA.

The researchers then searched for those parts of the DNA that were active in T-cells but inactive in B-cells. In this DNA, they found a gene that seemed to be completely rearranged in the different lines of T-cells they examined.

Davis and his colleagues determined the sequence of nucleotides in this purported T-cell receptor gene and found that it coded for a molecule with characteristics very similar to antibody.

Thus, T-cells seem to do their job of specifically recognizing foreign substances in the body with a molecule very similar to the B-cell antibody.

The scientists began the project as researchers at the National Institute of Allergy and Infectious Diseases (NIAID), a division of the National Institutes of Health in Bethesda, Maryland.

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EDITORS: Photos available on request.